

## REMARKS

### I. Status of the Claims

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1, 25 and 52 are currently amended, and claims 56-76 are added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

Exemplary support for the claim amendments and newly added claims is found the specification as indicated below. The amendments were made and the new claims were added to more clearly define claim scope.

| <u>Claim #</u> | <u>Exemplary Support</u>                    |
|----------------|---|
| 1              | Page 1, line 20                             |
| 52             | Page 8, lines 1-2                           |
| 56-57<br>(new) | Page 6, line 33, through page 7, line 2     |
| 58 (new)       | Original claims 1 and 17; page 6, lines 1-3 |
| 59 (new)       | Page 6, lines 16-19                         |
| 60-63<br>(new) | Original claims 1 and 17; page 6, lines 1-3 |
| 64-76<br>(new) | Page 6, line 33, through page 7, line 2     |

Upon entry of this Amendment, claims 1-76 will be pending in the application.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

### II. October 30, 2003 Teleconference

Applicants would like to thank Examiner Kam for clarifying the correct date on which Paper No. 8 was filed. On page 3 of the outstanding Office Action dated September 16, 2003, the Examiner refers to Paper 8 filed on November 27, 2002. During an October 30, 2003 teleconference with Applicant's representative, Examiner Kam confirmed that Paper No. 8 is Applicant's Amendment Under 37 C.F.R. § 1.111, dated June 10, 2002, a copy of which was faxed to the Examiner on November 1, 2003 and November 15, 2003. Applicant refers to this paper as "Paper No. 8" in the discussion provided below.

### **III. Claim Objections**

Claim 1 is objected to because the amended claim in the response filed on July 9, 2003 (Paper No. 12) is allegedly not based on the previously amended claim 1 filed in Paper No. 8. Applicant has amended claim 1 to be based on the previously amended claim 1 (Paper No. 8). This ground for objection is now moot.

### **IV. Claim Rejections - 35 U.S.C. § 112, Second Paragraph**

Claims 2-4, 17, 23-30, 34, 35, 37, 38, 41, 42, 44, 45 and 47-54 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. Applicant respectfully requests reconsideration and withdrawal of the rejection.

A. The Examiner asserts that in claims 2-4, 34, 35, 37, 38, 44, 45, 50 and 51, the terms "greater than about 6.0" and "greater than about 5.5" are allegedly indefinite.

B. The Examiner asserts that in claims 23-25, the terms "less than about 5%," "for up to at least 6 months," and "less than about 3 to about 4%" are allegedly indefinite.

C. The Examiner asserts that in claim 42, the term "no more than about 2%" is allegedly indefinite.

D. The Examiner asserts that in claim 48, the term "up to about 24 hours" is allegedly indefinite.

E. The Examiner asserts that in claim 17, the terms “one or more amino acid substitutions, additions, deletions or modifications” and “biological activity” are allegedly indefinite.

F. The Examiner asserts that in claims 49-54 the terms “a disorder, disease or condition” and “gastrointestinal disease” are allegedly indefinite.

G. Finally, the Examiner asserts that claims 49-54 are indefinite because the claims allegedly lack essential steps. The Examiner states that the omitted step is the outcome for the treatment.

All of the above-noted rejections were made by the Examiner in the Office Action dated March 8, 2002 (Paper No. 7), and were successfully overcome by Applicant’s arguments recited in Paper No. 8.

In the March 8, 2002 Office Action (Paper No. 7), items 7-12 recited rejections under 35 U.S.C. § 112, second paragraph, which are nearly identical to the rejections under 35 U.S.C. § 112, second paragraph, recited in the outstanding Office Action. In response to Applicant’s arguments recited in Paper No. 8, the Examiner stated: “[t]he previous rejection of claims 1-54, under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants’ amendment to the claims, and applicants’ response at pages 3-5 in Paper No. 8.” (See page 2 of the Examiner’s Office Action dated February 5, 2003 (Paper No. 10), under the heading “Rejections Withdrawn”). Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejections.

V. **Claim Rejections - 35 U.S.C. § 103**

A. **Rejection of Claims 1-10, 22 and 49-55 as Being Obvious over Knudsen et al. in view of Yamazaki et al.**

Claims 1-10, 22 and 49-55 are rejected under 35 U.S.C. § 103 as being allegedly obvious over Knudsen et al. (WO 99/43361, “Knudsen”) in view of Yamazaki et al. (USP 6,120,761, 102(e) date: December 16, 1998, “Yamazaki”). Applicant respectfully traverses and requests reconsideration and withdrawal of the rejection.

**1. The Examiner's Basis for the Rejection**

The Examiner asserts that it would have been obvious to a person of ordinary skill in the art to prepare a pharmaceutical composition of GLP-2 as indicated by Knudsen with the addition of histidine as a stabilizing agent as taught by Yamazaki to treat a gastrointestinal disease because using histidine as a stabilizing agent is safe without the risk of viral contamination and is also economically advantageous.

**2. There is no Motivation to Combine the Teachings of Knudsen and Yamazaki Because Yamazaki Relates to Erythropoietin, Which is Significantly Different Than Applicant's Claimed GLP-2**

A proper rejection for obviousness under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition, or device, or carry out the claimed process, and (2) whether the prior art would also have revealed that in making or carrying out the claimed invention, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art, and not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438 (Fed. Cir. 1991). In the present case, the examiner has failed to establish a *prima facie* case of obviousness for the following reasons.

There is no teaching or suggestion in the cited art to combine the teachings of Knudsen with the teachings of Yamazaki to obtain the claimed invention. Yamazaki is directed to a composition comprising erythropoietin, while the present invention is directed to a formulation comprising a naturally occurring GLP-2 or analog thereof. Erythropoietin and a naturally occurring GLP-2 or an analog thereof are not interchangeable, and have different properties and characteristics. The physical properties of each protein are so dramatically different that it is not intuitive that excipients and formulations that stabilize erythropoietin would have the same effect on naturally occurring GLP-2 or an analog thereof.

The chart provided below shows some of the different properties between GLP-2 and ALX-0600, an exemplary GLP-2 analog.

| <u>Property</u>              | <u>ALX-0600</u>   | <u>Erythropoietin</u>  |
|------------------------------|---|--|
| <i>Molecular weight (Da)</i> | 3752.1  | 30,400 (fully glycosylated protein)  |
| <i>Isoelectric point</i>     | 4.3   | 8.99   |
| <i>structure</i>             | essentially random coil, very little structure, no glycosylation, no disulfide bridging | glycoprotein, 4-helix bundle structure, one disulfide bridge   |
| <i>Amino acid sequence</i>   | HGDGSFSDEMNTILDNLAAR<br>DFINWLIQTKITD   | APPRLICDSRVLERYLLEAKEAE<br>NITTGCAEHCSLNENITVPDTKV<br>NFYAWKRMEVGQQAVEVWQG<br>LALLSEAVLRGQALLVNSSQPW<br>EPLQLHVDKAV<br>SGLRSLLTLLRALRAQKEAISPP<br>DAASAAPLRTITADTFRKLFRV<br>YSNFLRGKLKLYTGEACRTGDR |

Erythropoietin is a large glycoprotein (eight times the size of ALX-0600), with significant conformational structure. At a neutral pH, this protein will be positively charged. In contrast, the GLP-2 analog ALX-0600 is considered to be a small peptide, i.e., it has very little structure. At neutral pH (the pH of the formulation), the GLP-2 analog ALX-0600 will be negatively charged.

**3. There is no Motivation to Combine the Teachings of Knudsen and Yamazaki Because Many Problems may be Encountered in Designing Peptide/Protein Formulations**

Additionally, a person of ordinary skill in the art would know that there are several problems that may be encountered when designing peptide/protein formulations, as each protein is unique and the formulation depends on the physiochemical properties of the protein among other things.

Attached are Pikal et al., *Pharmaceutical Research*, 8(4):427-436 (1991) (Exhibit 1) and Cleland, J.L. and Langer, R. (1994) "Formulation and delivery of proteins and peptides: design and development strategies" in J.L. Cleland and R. Langer (Eds.), *Formulation and Delivery of Proteins and Peptides*. American Chemical Society, Washington D.C., p. 1-19 (Exhibit 2). These references detail the difficulties that may be involved with designing peptide/protein formulations. For example, Pikal et al. describe the difficulties that were encountered in determining a formulation for human growth hormone. *See e.g.*, Abstract. Cleland et al. describe the many variables that must be considered when designing a protein/peptide formulation, such as the isoelectric point, molecular weight, glycosylation or other post-translational modification, and overall amino acid composition (*see e.g.*, page 4, third full paragraph of Cleland et al.). Cleland et al. also note that "one parameter that impacts all the major degradation pathways is the solution pH." (*See e.g.*, page 5, first full paragraph). Additionally, in the paragraph bridging page 1 of Cleland et al. it states"

*The design and production of protein and peptide drug formulations is not well developed and many of the mechanisms for stabilization and delivery of these drugs have not been determined...Each molecule has its own unique physical and chemical properties which determine its in vitro stability.*

Because of the inherent difficulties in designing peptide/protein formulations, one of skill in the art at the time the claimed invention was made would not have been motivated to attempt to make Applicant's claimed invention, given the teachings of Knudsen and Yamazaki.

**4. One of Ordinary Skill in the Art Would Not Have had a Reasonable Expectation of Success in Obtaining the Claimed Invention by Combining the Teachings of Knudsen and Yamazaki**

A person of ordinary skill in the art would not have had a reasonable expectation of success in adding a stabilizing agent known to stabilize erythropoietin to a pharmaceutical formulation comprising a naturally occurring GLP-2 or analog thereof.

As discussed above, erythropoietin and GLP-2 have different properties and characteristics. Additionally, a person of ordinary skill in the art would know that there are several problems that may be encountered when designing peptide/protein formulations, as each protein is unique and the formulation depends on the physiochemical properties of the protein among other things. Thus, a person of ordinary skill in the art would not expect a naturally occurring GLP-2 or analog thereof to be stable under the same conditions as erythropoietin. At best, the examiner is using an improper "obvious to try" standard. However, "'obvious to try' has long been held to not constitute obviousness." *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210 (Fed. Cir. 1995).

**B. Rejection of Claims 11, 12, 31 and 33 as Being Obvious over Knudsen in view of Yamazaki and Further In View of Hora et al.**

Claims 11, 12, 31 and 33 are rejected under 35 U.S.C. § 103 as being allegedly obvious over Knudsen in view of Yamazaki as applied to claims 1-10, and further in view of Hora et al. (USP 5,997,856; "Hora"). Applicant respectfully requests reconsideration and withdrawal of the rejection.

As discussed above, the Examiner has failed to establish a *prima facie* case of obviousness for the rejection of the claims over Knudsen in view of Yamazaki. Hora does not remedy the deficiencies of Knudsen and Yamazaki. Hora discloses a method for the solubilization and/or stabilization of polypeptides using cyclodextrin. The claims of Hora are directed to a method for formulating IL-2. Hora fails to disclose the presently claimed combination of GLP-2, histidine, phosphate buffer, and a bulking agent. Therefore, claims 11, 12, 31 and 33 are not obvious over Knudsen in view of Yamazaki and further in view of

Hora. Applicant respectfully traverses and requests reconsideration and withdrawal of the rejection.

**C. Rejection of Claims 13-15, 17-20 and 32 as Being Obvious over Knudsen et al. In View of Yamazaki et al., and Hora et al., and Further In View of Drucker et al. (WO 97/39031)**

Claims 13-15, 17-20 and 32 are rejected under 35 U.S.C. § 103 as being allegedly obvious over Knudsen in view of Yamazaki and Hora as applied to claim 1, and further in view of Drucker et al. (WO 97/39031; "Drucker A"). Applicant respectfully requests reconsideration and withdrawal of the rejection.

As discussed above, the Examiner has failed to establish a *prima facie* case of obviousness for the rejection of the claims over Knudsen in view of Yamazaki and Hora. Drucker A does not remedy the deficiencies of Knudsen, Yamazaki and Hora. Drucker A discloses analogs of GLP-2, formulations comprising the analogs, and uses thereof. However, Drucker A fails to disclose the presently claimed combination of GLP-2, histidine, phosphate buffer, and a bulking agent. Therefore, claims 13-15, 17-20 and 32 are not obvious over Knudsen in view of Yamazaki and Hora and further in view of Drucker A. Applicant respectfully traverses and requests reconsideration and withdrawal of the rejection.

**D. Rejection of Claims 16 and 21 as Being Obvious over Knudsen In View of Yamazaki, and Further In View of Thim**

Claims 16 and 21 are rejected under 35 U.S.C. § 103 as being allegedly obvious over Knudsen in view of Yamazaki as applied to claim 1, and further in view of Thim et al. (USP 5,912,229; "Thim"). Applicant respectfully requests reconsideration and withdrawal of the rejection.

As discussed above, the Examiner has failed to establish a *prima facie* case of obviousness for the rejection of the claims over Knudsen in view of Yamazaki. Thim does not remedy the deficiencies of Knudsen and Yamazaki. Thim relates to use of a pharmaceutical composition comprising GLP-2 or an analog thereof. However, Thim fails to disclose the presently claimed combination of GLP-2, histidine, phosphate buffer, and a

bulking agent. Therefore, claims 16 and 21 are not obvious over Knudsen in view of Yamazaki and further in view of Thim. Applicant respectfully traverses and requests reconsideration and withdrawal of the rejection.

**E. Rejection of Claims 43-46 as Being Obvious over Knudsen In View of Yamazaki, and Further In View of Drucker et al. (USP 5,952,301; "Drucker B")**

Claims 16 and 21 are rejected under 35 U.S.C. § 103 as being obvious over Knudsen in view of Yamazaki as applied to claim 1, and further in view of Drucker et al. (USP 5,952,301; "Drucker B"). Applicant respectfully requests reconsideration and withdrawal of the rejection.

As discussed above, the Examiner has failed to establish a *prima facie* case of obviousness for the rejection of the claims over Knudsen in view of Yamazaki. Drucker B does not remedy the deficiencies of Knudsen and Yamazaki. Drucker B discloses pharmaceutical compositions of GLP-2 with at least one other peptide hormone, and uses thereof. However, Drucker B fails to disclose the presently claimed combination of GLP-2, histidine, phosphate buffer, and a bulking agent. Therefore, claims 16 and 21 are not obvious over Knudsen in view of Yamazaki and further in view of Drucker B. Applicant respectfully traverses and requests reconsideration and withdrawal of the rejection.

## CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Applicant has enclosed with this amendment a Petition for Extension of Time to make this response timely.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By Michele M. Simkin

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 672-5538  
Facsimile: (202) 672-5399

Michele M. Simkin  
Attorney for Applicant  
Registration No. 34,717